amendments herein, claims 2-4, 8-10, 12-14, and 18-24 will be pending. Applicant has also amended the specification to correspond to the amended claims.

Applicant maintains that support for these amendments to the claims and specification and the additional claims 22-24 can be found in the original application. Applicant has amended the language of claims 2, 3, and 18 to indicate that single bonds in alkyl groups may be replaced with double or triple bonds only when a sufficient number of carbon atoms are present to do so. As discussed below, support for such amendment can be found, for example, on page 14, lines 3-5 of the original specification.

In the method and composition claims, applicant has added "an inflammatory disease" to the list of disorders which can be treated by the subject CRF antagonists. The original specification indicates, on page 1, lines 29-34, that CRF antagonists are effective in the treatment of a wide range of stress-related illnesses and that, inter alia, inflammatory diseases are affected by CRF antagonists. Applicant also notes that the Examiner stated on page 2 of the Office Action that the compounds of the invention are "allegedly effective against . . . inflammatory disorders (e.g. allergies)".

Also, in the method and composition claims, applicant has replaced "acquired immune deficiency syndrome (AIDS)" with the phrase "human immunodeficiency virus infections" from the original application at, for example, page 14, line 18.

Applicant has included "psychosocial dwarfism" in the claims, support for which may be found on page 15, lines 2-3, and page 16, line 6, of the original application.

In claim 18, applicant has added terms to groups R^4 (triflouromethyl), R^5 (pyrimidyl), and R^{12} ((C_1-C_4 alkyl)O(C_1-C_4 alkyl), OCF_3, and fluoro). Support for such terms as possible R^4, R^5, and R^{12} groups can be found in the original application. For example, page 9, lines 9-15, includes trifluoromethyl as an option for R^4, pyrimidyl as an option for R^5, and (C_1-C_4 alkyl)O(C_1-C_4 alkyl), OCF_3, and fluoro as options for R^{12}. It is clear from the language of this section of the specification that these groups are also possible groups for the compounds of the subject invention (as set forth on page 1, line 35, through page 5, line 11), since the language on page 9 recites such groups to be substituents on compounds considered "other more specific embodiments of the invention". Since the compounds described on page 9 having such groups are "more specific embodiments of the invention", these groups are therefore possibilities for the compounds of the invention as a whole as described on pages 1-11. Applicant has added claim 22, which is of the same scope as claim 18 prior to entry of the above amendments, and

claims 23 and 24 which are composition and method claims, respectively, depending from claim 22, and therefore of the same scope as claims 20 and 21 prior to entry of the above amendments to claim 18.

Since support for the above amendments can be found in the original application, applicant maintains that these amendments do not raise an issue of new matter and respectfully requests that they be entered.

The Examiner rejected claims 2-5, 8-10, 12-14, and 18-21, each for various reasons, under 35 U.S.C. 112 rejection (first and second paragraphs) for alleged failure to describe the claimed invention in terms enabling any person skilled in the art to make and use the invention, and/or for alleged failure to particularly point out and distinctly claim the subject matter regarded as the invention. Applicant will address the various reasons for rejection individually.

The Examiner stated that the language in the claims for R^1, R^2, and R^5 which recites that single bonds in C_1-C_4 alkyl groups may be replaced by double or triple bonds is clearly erroneous. The Examiner correctly noted that a C_1 alkyl group has no carbon-carbon single bond to replace. Applicant has hence amended this language in the claims to recite that a single-bond may be replaced with a double or triple bond if there are at least two carbons present in the alkyl group, and that one or two single bonds may be replaced with double or triple bonds if there are at least four carbons present in the alkyl, and, in the case of R^2, which may be a C_1-C_{12} alkyl group, from one to three single bonds may be replaced with a double or triple bond if there are at least six carbons present. It is clear that this was the original intention, as indicated, for example, on page 14, lines 3-5 of the specification, which states that "whenever reference is made herein to C_1-C_4 alkyl or C_1-C_6 alkyl which 'may contain one double or triple bond' in the definitions of R^1 and R^4, it is understood that at least two carbons are present in the alkyl for one double or triple bond." It is clear from this statement that applicant intended a sufficient number of carbons to be present in any recited alkyl group containing one or more double or triple bonds. Applicant respectfully requests that this rejection be withdrawn in light of the amended language in the claims.

The Examiner also maintained that both "alkylthio" (which the Examiner stated as meaning -S(alkyl)), and "mercaptoalkyl" (which the Examiner stated as meaning -(alkyl)SH) to be reasonable possibilities for the original term "thioalkyl" recited for R^4 in the claims. The Examiner further asserted that the term "alkylthio", with which applicant has replaced the original term "thioalkyl", is new matter.

Applicant respectfully traverses. Applicant submits that the term "thioalkyl" has been allowed in the claims of many United States patents to represent an -S-alkyl group, which, as indicated in applicant's previous response, was applicant's intention when using the term in the originally filed claims. In support thereof, applicant submits herewith Spada et al. (U.S. Patent 5,561,134; October 1, 1996) and Miller et al. (U.S. Patent 5,541,054; July 30, 1996), also listed on the attached PTO-FB-A820. These patents both recite the term "thioalkyl" in the claims (see claim 1 of each patent). As demonstrated by the chemical structures spanning Columns 9 and 10 of Miller et al., "thioalkyl" in Miller et al. represents -S-alkyl (note the $-SCH_3$ groups in the chemical structures). In view of these patents, applicant submits that there exists basis for -S-alkyl groups in the original application and respectfully requests that the Examiner withdraw the aforementioned rejection.

The Examiner maintained that the clause in original claim 3 (page 51, lines 30-31, of the originally-filed application) "wherein each of the foregoing (C_1-C_4) alkyl groups may optionally contain one double or triple bond" finds no antecedent basis, rendering the claim improperly dependent, and finds no basis in the specification, rendering the claim non-enabled. According to the Examiner, claim 3 is broader than claim 18, even as amended from claim 1 in applicant's January 26, 1998 response, since R^5 in claim 3 includes pyridyl and pyrimidinyl, and since claim 3 also recites a C_1-C_4 alkyl in alkoxy, alkoxyalkyl, and hydroxyalkyl groups.

Applicant respectfully traverses the original grounds for rejection and has further amended claim 18 to overcome the lack of antecedent basis problem. Applicant has amended claim 18 so that all of the terms in claim 3 are recited. As discussed above, it is clear from the language of the original application (page 9, lines 9-15, for example) that such terms should be recited. Page 9, lines 9-15, of the original application states "other more specific embodiments of the invention include compounds of formulas I, II and III wherein . . ." and then goes on to recite a subgenus of compounds (set forth in claim 3), which includes the terms which are added to claim 18 above. Since the specification indicates that this subgenus constitutes "other more specific embodiments of the invention", it is clear that the possible groups for this subgenus are also possible groups for the compounds of the invention as a whole. Also, since the specification as originally filed explicitly indicates that this subgenus constitutes "other more specific embodiments of the invention", it is clear that the compounds within this subgenus have the utility attributed to the invention set forth in the original specification and also can be used as taught in the original specification. (The subject application sets forth a

utility for compounds of the invention and teaches how to use compounds of the invention at, *inter alia*, pages 33 through 34.) In light of these amendments to claim 18, and the above remarks, applicant respectfully requests that the rejection of claim 3 for a lack of antecedent basis and alleged lack of enablement for claim 3 be withdrawn.

Applicant has canceled the language which was added to page 4 of the specification in the January 26, 1998 response. Applicant has amended the specification instead so that the terms which are added herein to claim 18 are also inserted in the corresponding locations in the specification. Support for including such terms in the specification can be found in the original application for the same reasons given in the preceding paragraph for including the terms in claim 18.

The Examiner rejected claims 2-5, 8-10, 12-14, 18, 20 and 21 as allegedly being drawn to an improper Markush group. The Examiner stated that limiting the claims to pyrrolopyrimidines would overcome this rejection.

Applicant respectfully traverses this rejection. Applicant contends that the compounds as set forth in the claims as amended in applicant's previous January 26, 1998 response share a common pyrimidino-containing, nine-membered heterobicyclic nucleus which accounts for a substantial portion of their size and molecular weight and also share a common utility as CRF antagonists. The claimed compounds do not vary so much as to constitute different inventions, and this is supported by their similar classification. Accordingly, applicant requests that the rejection based on an alleged improper Markush group be withdrawn.

Regarding the rejection of claims 20 and 21 under 35 U.S.C. 112, first paragraph, for alleged failure to enable the full scope of the claims, applicant respectfully traverses for the following reasons.

The Examiner first maintained that the scope of the specific disorders recited in the claims is not enabled. The Examiner stated that an alleged failure in the medicinal sciences to date to obtain a compound or class of compounds able to treat the number of disorders recited in the claims places the burden on applicant to show that the claimed compounds can accomplish this. The Examiner stated that the claimed compounds are allegedly effective against a huge variety of psychological disorders, inflammatory disorders, for example allergies, neurodegenerative disorders, all chemical dependencies regardless of type, CNS disorders, such as stroke, and developmental disorders, such as dwarfism. The Examiner stated that the compounds are claimed to be useful in a number of basic systems of the body, such as the

cardiovascular system (for hypertension and tachycardia), the gastrointestinal system (for IBS, spastic colon, and ulcers), the joints (for rheumatoid arthritis), the immune system (for immune suppression), the muscular system (for muscular spasms), and the excretory system (for urinary incontinence). The Examiner stated that the compounds are claimed to be effective against disorders which are normally thought of as untreatable, such as multiinfarct dementia. According to the Examiner, the claimed genus of compounds has such a wide range of action as to constitute a general panacea, however, such a generalized panacea is not deemed enabled, citing In re Citron, 129 USPQ 520.

Applicant respectfully traverses. In re Citron does not stand for the proposition that there is a limit to the number of disorders which an applicant may claim to treat, as the Examiner seems to have implied. The Examiner suggests that, to date, there is no known "general panacea", and that a claim to a "general panacea" would require further evidence to patent. Applicant, however, is not claiming a "general panacea". Applicant is claiming a pharmaceutical composition and method for treating disorders which may be effected or their treatment facilitated by antagonizing CRF.

Although the Examiner has rejected the instant claims under 35 U.S.C. 112, the rejection appears to be based at least in part on the Examiner's opinion that applicant has not sufficiently established a utility for the claimed invention. However, courts have found that the mere identification of a pharmacological activity of a compound relevant to an asserted pharmacological use provides an "immediate benefit to the public" and this satisfies 35 U.S.C. 101. See Nelson v. Bowler, 206 USPQ 881 (CCPA 1980); Cross v. Iizuka, 224 USPQ 739 (Fed.Cir. 1985). In the instant case, applicant has found compounds which have CRF antagonistic activity, this being set forth at, for example page 34, lines 5-10, of the application.

CRF antagonism is relevant to many pharmacological uses, as evidenced by, for example, the references which the Examiner cited in the March 26, 1998 Office Action, namely Chalmers et al. and Stratakis et al. Chalmers et al. note that, in addition to a neuroendocrine role in the body's stress-response, CRF elicits a wide spectrum of autonomic, electrophysiological and behavioral effects that are consistent with a neurotransmitter and/or neuromodulator role in the brain. (See page 166, the first column, lines 10-18, of Chalmers et al.). Stratakis et al. note that corticotropin-releasing hormone is expressed widely in mammalian tissues, including the hypothalamus, brain and peripheral nervous system, lung, liver, gastrointestinal tract, immune cells and organs, gonads, and placenta. (See page 200, the

first column, lines 15-19). Thus, Chalmers et al. and Stratakis et al. suggest that CRF affects various systems throughout the body. Chalmers et al. indicate that increases in CRF are related to major depression and depressive illness (page 169, column 2, lines 20-33); anxiety-related disorders, such as panic disorder and generalized anxiety disorder (page 169, column 2, lines 34-44); eating disorders, inhibition of food consumption, anorexia nervosa (page 169, column 2, lines 45-58); ischaemic and excitotoxic brain damage (page 170, column 2, lines 1-2); and inflammation, arthritis, including rheumatoid arthritis (page 170, column 2, lines 7-19, and page 171, first column, lines 7-11). Stratakis et al. indicate that increases in CRF are related to tachycardia, hypertension, melancholic depression, anorexia nervosa, panic anxiety, obsessive-compulsive disorder, chronic active alcoholism, alcohol and narcotic withdrawal, sexual abuse, excessive exercising, and malnutrition (see page 204, second column); "euthyroid sick" syndrome, chronic inflammatory disease (page 205, second column); suppression of GHQ, which is indicated as related to short stature (page 205, second column, through 206, first column); and stimulation of colonic transit and fecal excretion, and gastric stasis (page 206, first column, lines 22-45). Abreu et al. (U.S. Patent 5,063,245) indicate that CRF antagonists can be used to treat stress-related disorders, including anxiety, panic disorder, obsessive-compulsive disorder, abnormal aggression, stress-induced cardiovascular abnormalities (e.g., unstable angina and reactive hypertension), anorexia nervosa, bulimia, irritable bowel syndrome, and to treat alcohol and drug withdrawal, and epilepsy (column 5, lines 8-20). Rivier et al. (U.S. Patent 4,605,642) indicate that CRF antagonists could ameliorate stress-induced conditions to which endogenous CRF might contribute, including some types of hypertension, infertility, decreased libido, impotency and hyperglycemia (column 12, lines 48-52). Rivier et al. further indicate that CRF antagonists can be used to influence memory, mood, pain appreciation, and depression and/or anxiety (column 12, lines 52-61). Toshihiro, S., et al. and Shuso, S. et al. indicate a connection between CRF activity and hypoglycemia.

The Examiner further specified particular disorders recited in the claims, stating that such disorders have not heretofore been treatable generally, or are extremely difficult to treat. In that regard, the Examiner mentioned "cancer", "chemical dependencies and addictions" "AIDS", "Alzheimer's disease", and "stroke". The Examiner cited Chalmers et al. and Stratakis et al. as supposed evidence.

Applicant respectfully traverses. True, certain utilities may warrant further evidence for enablement than would be otherwise required, Ex parte Stevens, 16 USPQ2d 1379. However,

applicant maintains that the description provided in the application is sufficient to enable treatment of the disorders which are recited in the above claims. With respect to these disorders, applicant maintains that treating these disorders is supported by the original application. A connection between CRF antagonism and stroke and between CRF antagonism and treating chemical dependency and addiction is indicated in the art (see page 170, first column , last line, through second column, first line, of Chalmers et al. for stroke; and page 204, second column, lines 34-35, of Stratakis et al. for chemical dependency and addiction). A connection between cancer and stress-induced hormones has also been indicated (see, Fackelmann, K.A., and Raloff, J., Psychological Stress Linked to Cancer, Science News (1993), Vol. 144, p. 196). Furthermore, a connection between CRF and the immune system has also bee indicated (see, e.g., Owens, M.J., and Nemeroff, C.B., Physiology and Pharmacology of Corticotropin-releasing Factor, Pharm. Rev., Vol. 43, pp. 425-473, 444). The same is true for other disorders recited in the claims: they too have been indicated in the art to be affected by CRF activity, as discussed above. Moreover, Chalmers et al. note with respect to treating stroke, "Recent data indicate that peptide antagonists of CRF receptors can inhibit ischaemic and excitotoxic brain damage." (See page 170, first column through second column, of Chalmers et al.).

With respect to chemical dependency and withdrawal, applicant submits as part of the Information Disclosure Statement, information on TRANXENE (clorazepate dipotassium), indicated for the symptomatic relief of acute alcohol withdrawal, and REVIA (naltrexone hydrochloride tablets), indicated for treating alcohol dependence and blocking the effects of exogenously administered opioids. Applicant notes that it remains the Patent Office's burden to provide reasons why claimed compounds would not be expected to work for treating any particular disorder. In re Bowen, 181 USPQ 48, 50-51 (CCPA 1974); U.S. v. Telectronics Inc., 8 USPQ2d 1217, 1223-1224 (Fed.Cir. 1988). The Examiner has not pointed out any evidence that "cancer", "HIV infection" "drug and alcohol withdrawal symptoms", or "chemical dependencies and addictions" are incredible to treat. Since applicant has ascertained compounds having CRF antagonizing activity which is linked to the disorders recited in the claims, and since the Examiner has not provided any evidence to doubt that these disorders can be treated, it is respectfully requested that this rejection be withdrawn.

The Examiner also stated that AD (Alzheimer's disease) and eating disorders, including obesity and anorexia nervosa are associated with abnormally low levels of CRF and that administering a CRF antagonist would be expected to "make matters worse".

Applicant respectfully traverses. Contrary to the Examiner's assertion, anorexia nervosa is associated with high levels of CRF, as indicated by, for example, Chalmers et al. (page 169, second column, lines 47-56). Concerning Alzheimer's disease and obesity, the prior art, including Chalmers et al., indicates a connection between CRF and these disorders. As another example, WO 95/34563 indicates that CRF antagonists are useful for treating disorders including Alzheimer's disease and obesity (see page 6, line 7 and line 13, of WO 95/34563). Nothing in Chalmers et al. appears to establish that the claimed CRF antagonists would not be able to treat obesity or Alzheimer's Disease. Although Chalmers et al. does state (page 169, second column) "evidence from animal studies suggests that low levels of CRF may be associated with the development of obesity syndromes," this does not mean that no obesity disorder, for example, obesity resulting from anxiety or depression, can be treated by a CRF antagonist or that no obesity disorder is facilitated by CRF activity. With respect to Alzheimer's disease, Chalmers et al. state:

> "Several studies have provided evidence in support of alterations in CRF in Alzheimer's disease. There are decreases in CRF content, reciprocal increases in CRF receptors, and no significant alteration in CRF-binding protein" (page 170, first column).

Nothing in this statement establishes that a CRF antagonist would not assist in treating Alzheimer's disease; this statement merely adds support to their being a connection between CRF activity and Alzheimer's disease and that a CRF antagonist may be useful against such disorders.

The Examiner also stated that replacement of the term "HIV infections" with "AIDS" is new matter. Applicant has removed "AIDS" from the claims and reinserted "human immunodeficiency virus infections". Applicant traverses the original grounds for rejection, which was that "HIV infections" is not a disorder. In that regard the Examiner stated "AIDS is a disorder, not HIV infection" (see page 6 of the July 25, 1997 Office Action). Applicant requests further explanation: how is HIV infection not a disorder? It is common knowledge that a disorder can mean a disturbance of normal physical or mental health (see page 399 of The

American Heritage College Dictionary). Applicant contends that an HIV infection is a disturbance of normal physical health; due to the ability of HIV to handicap a person's immune system, a person with an HIV infection may take precautions and measures to boost his or her immune system and to minimize exposure to other infectious diseases. This is something an uninfected person need not do, and therefore it is out of the ordinary and a "disorder". In light of these remarks, applicant respectfully requests that the Examiner withdraw such rejection.

The Examiner also stated that deleting "psychosocial" before the term "dwarfism" broadens the term "dwarfism". Applicant has reinserted the term "psychosocial" prior to "dwarfism". Applicant maintains that the term "psychosocial" is a well known term as evidenced for example by the definition provided in The American Heritage College Dictionary, included as part of the Information Disclosure Statement. "Psychosocial" is defined as "involving aspects of social and psychological behavior". Thus, "psychosocial dwarfism" is "dwarfism involving aspects of social and psychological behavior". Stratakis et al. indicate stress-induced release of CRF has been implicated in, as mentioned above, lower body growth and short stature (page 205, second column, through 206, first column). Applicant respectfully requests that the Examiner reconsider and withdraw this rejection.

The Examiner also stated that claims 20 and 21 are rejected under 35 U.S. 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter regarded by applicant as the invention. The Examiner asserted that the language "a disorder the treatment of which can be effected or facilitated by antagonizing CRF" is vague. The Examiner asserted that determining the scope of this term would involve extensive and potentially open-ended research. The Examiner presented a hypothetical in which a CRF antagonist "X" is administered to a patient with a disease "D", and in which the patient "D" does not respond to the antagonist "X". The Examiner questioned in such a case how does one conclude that disease "D" cannot be effected or facilitated by antagonizing CRF. The Examiner stated that the wrong dosage may have been used, another antagonist "Y" may be more potent and able to treat "D", that response to an antagonist might be attributed to an activity other than CRF antagonism, that the antagonist may induce a response if combined with another drug "Z", or that other individuals with "D" might respond.

Applicant respectfully traverses. First, the Examiner cannot require applicant to test each and every embodiment of the invention. See In re Bundy, 209 USPQ 48 (CCPA 1981). Also, different dosages can be tried to ascertain whether or not the disease responds to CRF

antagonism, and a suitable population of individuals can be tested; this does not constitute undue experimentation and is well within the present skill in the art and is required anyway by the U.S. Food and Drug Administration for any drug which is to be permitted to be prescribed. Asking applicant to anticipate how each individual would respond to each species of the invention is an unreasonable requirement on the Examiner's part. Moreover, the Examiner's statement that "literally speaking, any disorder can be treated with any drug, although the treatment might not be successful" and that applicant establish a criterion for "successful treatment" would, if followed by the Patent Office, render virtually every useful drug unpatentable absent human clinical data. Such data, numerous courts have held, is not required in order to obtain a patent (see, for example, Nelson v. Bowler and Cross v. Iizuka, supra).

Second, another way to determine if a disease or disorder is a product of CRF concentrations, is to see what responses are induced when laboratory animals are administered CRF, or to test for elevated CRF concentrations in laboratory animals or humans exhibiting suspected disorders or behaviors. Much of this type of analysis has already been done, as described in Chalmers et al. and Stratakis et al.

In sum, applicant submits that the claims are directed to an enabled and useful invention, and that all pending claims, as amended, comply fully with the provisions of 35 U.S.C. §112. Applicant therefore requests that all pending claims, as amended, be allowed to issue.

If a telephone interview would be of assistance in advancing prosecution of this application, the Examiner is invited to telephone applicant's attorney at the telephone number below.

Although no fee is believed necessary for filing this Preliminary Amendment, if a fee is found necessary in connection with filing this Amendment, authorization is hereby given to charge such fee to Deposit Account No. 16-1445.

Respectfully submitted,

Date: July 7, 1998

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